

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number  
**WO 01/10402 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 7/48** **Francesco; Via Cerato, 14, I-35122 Padova (IT). MARCOLONGO, Gabriele; Via Strade Interne, 3, I-35020 Due Carrare-Padova (IT).**
- (21) International Application Number: **PCT/IT99/00258**
- (22) International Filing Date: **6 August 1999 (06.08.1999)** (74) Agents: **LONG, Giorgio et al.; Jacobacci & Perani S.p.A., Via Senato, 8, I-20121 Milano (IT).**
- (25) Filing Language: **Italian** (84) Designated States (regional): **European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).**
- (26) Publication Language: **English**
- (71) Applicant: **INNOVET ITALIA S.R.L. [IT/IT]; Via Egadi, 7, I-20144 Milano (IT).** Published:  
— *With international search report.*
- (72) Inventors: **COMELLI, Cristina; Via dei Mille, 24, I-35141 Padova (IT). DELLA VALLE, Maria, Federica; Via Lepanto, 9, I-35141 Padova (IT). DELLA VALLE,** *For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



**WO 01/10402 A1**

(54) Title: **USE OF N,N'-BIS(2-HYDROXYETHYL)NONANDIAMIDE AS A COSMETIC AGENT**

(57) Abstract: The present invention relates to the use of N,N'-bis(2-hydroxyethyl)nonandiamide, the common international name of which is adelmidrol, as a cosmetic agent for use on skin and/or mucous membranes which are irritable and/or are subject to acute irritation, in man and in animals. The present invention also relates to a method for the preparation of N,N'-bis(2-hydroxyethyl)nonandiamide, comprising the reaction of azelaic acid or of a diester thereof with ethanolamine in an inert atmosphere, possibly on the presence of an inert solvent. This method enables adelmidrol to be produced in a particularly pure form suitable for its use in the cosmetic field.

USE OF N,N<sup>1</sup>-BIS(2-HYDROXYETHYL)NONANDIAMIDE AS A COSMETIC AGENT

The present invention relates to the use of N,N<sup>1</sup>-bis(2-hydroxyethyl)nonandiamide, the common international name of which is adelmidrol, as a cosmetic agent for use on skin and/or mucous membranes which are irritable and/or are subject to acute irritation, in man and in animals.

The term "cosmetic products" means all preparations which can protect or keep in good condition the external surfaces of the human or animal body such as the epidermis, the piliferous system and the hair, the nails, the lips, the external genital organs, and the mucous membranes of the mouth.

The basic role of the skin and of the mucous membranes is to protect the underlying tissues from potentially harmful environmental agents and to prevent excessive loss of fluids from the body. The barrier function of the tegumentary tissues is due mainly to the proteinaceous and, above all, to the lipid characteristics of their multi-layered epithelia (Gniadecha M. et al., 1998, J. Inv. Dermatol. 110: 393-398). The most superficial epidermal and/or epithelial

layers in fact protect against loss of water and provide an effective barrier which resists the entry of micro-organisms (Eliás P.M., 1988. Drug. Dev. Res. 13: 97-105).

It is known that this barrier function depends to a large extent on the proliferative and differentiatinal processes of the epidermal keratinocytes of the skin and of the epithelial cells of the mucous membranes (Brod J., 1991, Int. J. Dermatol., 30: 84-90).

It is known that the hydration state of the skin is a parameter which can easily be measured by non-invasive methods applied to the skin surface (Thune P., 1989, Acta Derm. Venereol., suppl. 144: 133-135). The quantitative measurement of the hydration state of the skin utilizes basically two measurements: transepidermal evaporation of water (TEWL) and skin capacitance.

TEWL, which is measured by an instrument known as an atmometer, expresses, in  $\text{g/m}^2/\text{hour}$ , the gradient of diffusion of water vapour through the epidermal tissue, given the known tendency of this gas to diffuse in accordance with the concentration gradient (Pinnagoda J. et. al., 1990, Contact Dermatitis, 22: 164-178). The water content of the *stratus corneum*, on the other hand, is expressed by electrical capacitance measured by the application of a corneometer which records the water

content on the surface of the skin, since water has the highest dielectric constant of all the skin components. An increase in skin water content brings about an increase in capacitance values which are expressed in arbitrary units by the corneometer (Werner Y., 1986, *Acta Derm. Venereol.*, 66: 281-284).

It is known that the determination of the skin hydration level by measurement of the TEWL enables subjects with skin which is normally reactive to very diverse stimuli to be distinguished from subjects characterized by an irritable skin (Tupker R.A., 1990, *Br. J. Dermatol.*, 123: 199-205).

It has been shown that the skin of atopic subjects is irritable in response to exogenous stimuli applied at skin level; in these subjects, the skin tends to appear dry (Tupker R.A. et al. 1990, *Br. J. Dermatol.*, 123: 199-205). These characteristic behaviours correspond to an altered barrier function and to an increase in TEWL values (Seidenari S. et al., 1995, *Acta Derm. Venereol.*, 75:429-433; Gollhausen R., 1991, in Ruzicka T. et al., eds., *Handbook of Atopic Eczema*, Springer Verlag, pp. 306-318; Thune P., 1989, *Acta Derm. Venereol.*, suppl. 144: 133-135; Werner Y. et al., 1985, *Acta Derm. Venereol.*, 65: 102-105; Berardesca E. et al., 1990, *Acta*

Derm. Venereol., 70: 400-404).

It has been shown that, in subjects with irritable skin, the TEWL is increased in comparison with normally responsive subjects. It is also known that this parameter increases further as a result of exposure of the irritable skin to hyper-reactive stimuli and that this phenomenon is frequently associated with the development of superficial skin reactions which alter epidermal appearance (Di Nardo A. et al., 1998, Acta Derm. Venereol., 78: 27 -30). It is also known that, in these conditions, a mechanical rubbing action, or the superimposition of several stimuli such as, for example, the hyper-reactive amplification produced by contact with allergenic substances used in daily hygiene, both in man and in animals, bring about progression towards epidermal lesions which are easily infected.

Even in normal conditions, irritable skin has clear unsightly effects which are generally recognizable in the form of dryness (Di Nardo A. et al., 1998, Acta Derm. Venereol., 78: 27-30) or of thinning of the skin which easily predispose to the development of loss of epithelium.

Irritable skin has therefore been defined as the epidermal functional state which characterizes a

population of predominantly healthy subjects in certain paraphysiological situations (ageing, pregnancy, menopausal states, pre-menstrual and post-menstrual situations, etc.).

Irritable skin and/or mucous membrane is a tissue which is easily predisposed to hyper-reactive symptoms in response to a diversified set of exogenous stimuli. As a result of stimuli of a neurogenic, immunogenic, physical (for example, radiation), chemical (for example, detergents, solvents, dyes, etc.), mechanical and/or traumatic nature, irritable skin easily develops clear signs of irritation with consequent unsightly effects (Ansel J.C., 1996, J. Invest. Dermatol., 106: 198-204).

It is also known that, precisely because of the altered barrier function and of the altered proliferative and differentiatinal process, whether it be epidermal or mucosal, irritable skin is predisposed to the development and progression of microbial infections both fungal and bacterial (Leibovici V. et al., 1995, Clin. Exp. Dermatol., 20: 390-394). It is also known that the altered cutaneous and mucosal barrier function explains a large proportion of recurrent and relapsing hyper-reactive episodes in the course of - or as a result of - microbial infections with particular reference to the

palmar and plantar skin locations as well as the vulvar and preputial locations.

In the presence of irritable skin and/or mucous membrane, the identification of molecules which re-establish the TEWL values which are functional in keeping the cutaneous and/or mucosal barrier in good condition, offering a modification and a protection from unsightly effects associated with irritable cutaneous and/or mucosal states, is therefore of considerable interest for the production of preparations for cosmetic use which are free of potential hyper-reactive stimulation effects and consequently do not result in adverse reactions due to contact.

It has surprisingly been found that adelmidrol (N,N'-bis(2-hydroxyethyl)nonandiamide) can lower abnormally raised TEWL values in subjects (human or animal) with skin and/or mucous membranes which are irritable and/or subject to acute irritation. It is therefore clear that adelmidrol can advantageously be used as a cosmetic agent or additive for the preparation of cosmetic compositions suitable for subjects with skin and/or mucous membranes which are irritable and/or subject to acute irritation.

The cosmetic effectiveness of adelmidrol is

demonstrated by the following example.

EXAMPLE A

TEWL was measured with the use of atmometer model EP1 (ServoMed - Sweden) which is based on estimation of the water-vapour gradient. All of the TEWL measurements were taken in accordance with the method described in Pinnagoda J. et al., 1990, Contact Dermatitis, 22: 164-178.

The measurements were taken on two groups of volunteer subjects, divided into:

- n=10 subjects aged between 25 and 29 years, who were normally reactive from a cutaneous point of view, without previous medical history of adverse reactions due to contact, or of atopia;

- n=10 subjects aged between 65 and 70 years, without previous medical history of dermatitis due to contact, or of atopia.

The areas of topical application of the experimental preparations and of TEWL measurement corresponded to circular areas of skin approximately 2 cm in diameter located in the medial volar region of the right forearm and spaced at least 2 cm apart. The corresponding areas of skin of the medial volar region of the left forearm were used as non-treated controls, upon each analysis.



The various preparations were applied in accordance with the following scheme:

(a) excipients alone (Example 1 of cosmetic preparations)

(b) complete preparation (Example 1 of cosmetic preparations containing 2% of adelmidrol)

(c) sodium lauryl sulphate (SLS) 5% as irritant

(d) 5% SLS + (a)

(e) 5% SLS + (b)

Preparations (a) - (e) were applied for 10 consecutive days. After application, each individual area treated was covered with a plaster. The TEWL measurements were taken on day 1 and on day 10, 1 hour after topical application of the preparations, after the plaster had been removed and the area had been cleaned with absorbent paper.

The data, expressed as Mean  $\pm$  SEM are summarized in the following table.

TABLE - TEWL values determined in young and elderly subjects (irritable skin) with and without treatment with adelmidrol

	young subject		elderly subject	
	DAY 1	DAY 10	DAY 1	DAY 10
base measurement	$4.06 \pm 0.98$	$4.10 \pm 1.02$	$7.52 \pm 1.05$	$7.50 \pm 1.15$
(a)	$4.15 \pm 0.85$	$4.23 \pm 0.92$	$7.23 \pm 1.01$	$7.45 \pm 1.08$
(b)	$4.09 \pm 0.95$	$4.10 \pm 0.82$	$6.08 \pm 0.96$	$5.20 \pm 0.86$
(c)	$4.10 \pm 0.70$	$20.35 \pm 2.41$	$8.05 \pm 1.15$	$47.26 \pm 2.85$
(d)	$4.15 \pm 0.70$	$20.35 \pm 2.41$	$8.05 \pm 1.15$	$47.26 \pm 2.85$
(e)	$4.05 \pm 0.85$	$6.80 \pm 1.86$	$7.25 \pm 1.05$	$8.32 \pm 2.06$

It is clear from the data shown in the table that adelmidrol can practically normalize TEWL values in subjects with irritable skin (elderly patients), bringing the TEWL from a base value of 7.50 ( $\pm 1.15$ ) which is abnormally high, to a value of 5.20 ( $\pm 0.86$ ) which is close to normality.

Moreover, adelmidrol brought about a clear reduction in TEWL values in both patients with normal skin (young patients) and patients with irritable skin (elderly patients), whose skin had been irritated acutely by

contact with 5% SLS.

As stated above, a reduction in TEWL values enables the unsightly effects associated with an irritated and/or irritable skin (dry skin, reddening) to be resisted. Adelmidrol can consequently be used advantageously as a cosmetic agent in the treatment of skin and/or mucous membranes which are irritable and/or are subject to acute irritation.

#### EXAMPLES OF COSMETIC PREPARATIONS

In all of the following examples, the initials OE mean "oxyethylenate".

##### Example 1 - Face and body cream

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	2.0 g
Vitamin E acetate	4.0 g
sodium hyaluronate	0.04 g
bronopol	0.005 g
hydrogenated castor oil 40 (OE)	1.5 g
noveon AA1	1.6 g
o-phenylphenol	0.18 g
aroma	0.15 g
water to make up to 100 g	

Example 2 - body milk

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	1.4 g
glycerol	5.0 g
Vaseline oil	3.0 g
silicone oil	1.0 g
gliceryl monostearate	1.4 g
cetostearyl alcohol	2.8 g
stearic acid	2.8 g
polyethylene glycol-soya sterols	6.0 g
carbomer	0.12 g
bronopol	0.05 g
aroma	0.05 g
water to make up to 100 g	

Example 3 - gel for oral use

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	1.0 g
glycerol	10.0 g
glycolic extract of	
echinacea purpurea	12.0 g
sodium alginate	2.5 g
sodium hyaluronate	0.04 g

bronopol	0.1 g
triclosan	0.3 g
water to make up to 100 g	

Example 4 - lotion for trichological use

100 g contains:

N,N <sup>i</sup> -bis(2-hydroxyethyl)nonandiamide	0,2 g
sodium hyaluronate	0,01 g
biotin	0,03 g
ethyl alcohol	30,0 g
aroma	0,02 g
water to make up to 100 g	

Example 5 - vaginal gel

100 g contains:

N,N <sup>i</sup> -bis(2-hydroxyethyl)nonandiamide	1.5 g
vitamin A palmitate	0.2 g
2-phenyl ethanol	0.15 g
glycerol	10.0 g
hydrogenated castor oil 40 (OE)	1.0 g
methyl paraoxybenzoate	0.1 g
noveon AA1	1.0 g
sodium hyaluronate	0.08 g
aroma	0.2 g

water to make up to 100 g

Example 6 - vaginal wash

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	0.4 g
vitamin A palmitate	0.02 g
2-phenyl ethanol	0.15 g
lactic acid	2.0 g
glycerol	6.0 g
hydrogenated castor oil 40 (OE)	0.4 g
methyl paraoxybenzoate	0.1 g
sodium hyaluronate	0.01 g
aroma	0.15 g
water to make up to 100 g	

Example 7 - intimate soap

100g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	0.5 g
triclosan	0.25 g
vitamin E acetate	0.05 g
lactic acid	1.0 g
rutin	0.02 g
bronopol	0.1 g
coco diethanolamide	2.5 g

undecylenic acid	0.2 g
glycolic extract of	
Echinacea purpurea	5.0 g
sodium lauryl (1-4)OE sulphate	20.0 g
disodium lauryl (1-4)OE sulphosuccinate	7.0 g
aroma	0.02 g
hydrogenated castor oil 40 (OE)	1.4 g
water to make up to 100 g	

Example 8 - deodorant stick

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	2.0 g
sodium hyaluronate	0.05 g
zinc ricinoleate	1.0 g
triclosan	0.25 g
vitamin E acetate	0.5 g
ethyl alcohol	30.0 g
bronopol	0.05 g
carbomer	1.5 g
polyvinyl alcohol	0.2 g
hydrogenated castor oil 40 (OE)	2.5 g
aroma	1.0 g
water to make up to 100 g	

Example 9 - nail drops

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	1.5
urea	10.0
hydrogenated castor oil 40 (OE)	5.0
vitamin A palmitate	0.3
undecylenic acid	0.2
biotin	0.6
benzyl alcohol	1.2
glycolic extract of	
Echinacea purpurea	10.0
acetone	8.0
isopropyl alcohol	36.0
water to make up to 100 g	

Example 10 - cream for podiatric use

100 g contains:

N,N <sup>1</sup> -bis(2-hydroxyethyl)nonandiamide	2.0
biotin	0.01
glycolic extract of	
Echinacea purpurea	10.0
usnic acid	0.2
zinc ricinoleate	2.0
isopropyl myristate	0.5



polyethylene glycol-soya sterols	4.0
stearic acid	2.5
cetostearyl alcohol	2.5
glyceryl monostearate	1.0
silicone oil	1.0
Vaseline oil	2.5
triclosan	0.2
bronopol	0.03
aroma	0.5
water to make up to 100 g	

It has also been found that the cosmetic effect of adelmidrol is performed especially if the product has a high degree of purity. In particular, an absence of potentially harmful impurities prevents the compound itself from causing undesired irritative reactions on the skin. A further subject of the present invention is therefore a method which enables extremely pure adelmidrol to be produced.

This method provides for the reaction of azelaic acid or a diester thereof with ethanolamine, with refluxing, in an inert atmosphere, possibly in the presence of an inert solvent. Preferred solvents for the azelaic acid reaction are xylene or toluene, particularly

xylylene. Preferred reaction temperatures are between 110°C and 145°C. Dimethyl, diethyl or dipropyl esters, preferably dimethyl ester, may be used as the diester of azelaic acid.

The method may also provide for a step for crystallization of the crude product from isopropanol, in which the crystallizate is subjected to a crumbling process at approximately 45°C for 4-8 hours, and to subsequent gradual cooling to 5-7°C over a period of 10-20 hours. This crystallization step enables a particularly pure product to be produced.

A further improvement in the purity of the adelmidrol can be achieved by subjecting the crystallizate to a drying step comprising a first drying stage at a pressure lower than 30 mmHg and at a temperature of between ambient temperature and 40°C for 24-72 hours, a second drying stage under the same conditions as described above but in a slightly acid atmosphere such as that obtained by placing a container containing a dilute solution of sulphuric acid in the dryer, and a third drying stage at a pressure of 1-2 mmHg and at a temperature of 25-40°C for a period of between 1 and 3 days.

The diester of azelaic acid is prepared with a

practically quantitative yield by reaction of azelaic acid with a primary aliphatic alcohol, hot, in the presence of an acid catalyst (Vogel, Chimica Organica Practica, Ed. Casa Editrice Ambrosiana, Milan 1988). The preferred alcohols are methyl, ethyl and propyl alcohols, most preferably methyl alcohol.

Two examples of preparations in accordance with the method of the present invention are given by way of indication below.

Preparation 1 - synthesis of adelmidrol from azelaic acid

47.05 g of azelaic acid (250 mmoles) and 45.8 g of ethanolamine (750 mmoles) were dissolved in 130 ml of xylene and heated with refluxing for 6 hours in a reactor with a reflux condenser and a Dean-Stark separator. The atmosphere in the reactor was rendered inert with nitrogen at atmospheric pressure. The mixture was then evaporated to dryness under vacuum. The residue was dissolved in 250 ml of pure isopropanol, the solution was then cooled to trigger crystallization, the crystallizate was then subjected to a crumbling process with stirring at 45°C for 6 hours. The crystallization was completed by subsequent slow cooling to 5-7°C over a period of 15 hours. The crystallizate was separated by filtration,

cold, in an inert atmosphere, washed three times with 30 ml of cold isopropanol and finally dried in a high degree of vacuum.

The drying was performed in stages as described below. The crystallizate, taken up in solvent, was stratified in polished stainless-steel trays and placed in a drying cabinet for static drying for two days at 30°C and at a pressure lower than 30 mmHg. Trays containing an approximately 1 M solution of sulphuric acid in water were then placed in the drying cabinet for 24 hours, again with a pressure lower than 30 mmHg. Drying was then completed under a vacuum of 1-2 mmHg for 2 days at 30°C.

The reaction yields were greater than 96%, with a recovery of more than 90% of pure product after crystallization and drying.

The profile of the impurities of the finished product was as follows:

free azelaic acid	<0.5%
monoethanolamide	<0.5%
free ethanolamine	<0.1%
isopropanol	<200 ppm
homologous diamides	1-10% (*)
2-oxazoline	absent

(\*) according to the quality of the starting azelaic acid

Preparation 2 - synthesis of adelmidrol from azelaic acid dimethyl ester

54.1 g of the dimethyl ester of azelaic acid (250 mmoles) and 33.6 g of ethanolamine (550 mmoles) were heated to 110°C for 7 hours in a reactor with a reflux condenser. The atmosphere in the reactor was rendered inert by nitrogen at atmospheric pressure. The mixture was then evaporated to dryness under vacuum. The residue was dissolved in 250ml of pure isopropanol, the solution was then cooled to trigger crystallization and the crystallizate was subjected to a crumbling process with stirring at 45°C for 6 hours. The process was completed by subsequent slow cooling to 5-7°C over a period of 15 hours. The crystallizate was separated by filtration, cold, in an inert atmosphere, washed three times with 30 ml of cold isopropanol and finally dried in a high degree of vacuum.

The drying was performed in stages as described below. The crystallizate, taken up with solvent, was stratified in polished stainless-steel trays and placed in a drying cabinet for static drying for two days at

30°C and at a pressure lower than 30 mmHg. Trays containing an approximately 1M solution of sulphuric acid in water were then placed in the drying cabinet for 24 hours, again with a pressure lower than 30 mmHg. Drying was then completed under a vacuum of 1-2 mmHg for 2 days at 30°C.

The reaction yields were again greater than 96%, with a recovery of more than 90% of pure product after crystallization and drying.

The profile of the impurities of the finished product was as follows:

free azelaic acid	<0.1%
monoethanolamide	<0.2%
free ethanolamine	<0.1%
isopropanol	<200 ppm
homologous diamides	<1%
2-oxazoline	absent

The method described above thus has the advantage of leading to a final product which is characterized by a high degree of purity, with higher yields than can be obtained by known methods (for example, see EP 0 550 0008 A2) and with lower running costs by virtue of the lower reaction temperatures (no greater than 145°C in

comparison with 160°C described in the known methods).

The reaction starting with the diester of azelaic acid has the further advantage of permitting purification even at the level of the starting product by fractional distillation of the diester. The lower and higher homologues of azelaic acid which are always present in considerable quantities in commercial azelaic acid (titre between 80 and 90%) can thus be eliminated.

## CLAIMS

1. Use of N,N<sup>1</sup>-bis(2-hydroxyethyl)nonandiamide as a cosmetic agent for skin and/or mucous membranes which are irritable and/or are subject to acute irritation.
2. Use according to Claim 1, as an agent which can lower abnormally raised TEWL values in skin and/or mucous membranes which are irritable and/or are subject to acute irritation.
3. Use according to Claim 1 or Claim 2, for the cosmetic treatment of the skin of the face, of the body, of the hands, of the feet, of the genital organs, and of the mucous membrane of the mouth, of the vagina and of the glans.
4. Use of N,N<sup>1</sup>-bis(2-hydroxyethyl)nonandiamide for the preparation of a cosmetic preparation.
5. A cosmetic composition containing N,N<sup>1</sup>-bis(2-hydroxy-ethyl)nonandiamide together with other cosmetic additives.
6. A cosmetic composition according to Claim 5, selected from the group comprising face and body cream, body milk, gel for oral use, lotion for trichological use, vaginal gel, vaginal wash, intimate soap, deodorant stick, nail drops, cream for podiatric use.



7. A cosmetic composition according to Claim 5 or Claim 6, containing from 0.2 to 2 grams of N,N<sup>1</sup>-bis(2-hydroxyethyl)-

nonandiamide per 100 grams of composition.

8. A method of preparing N,N<sup>1</sup>-bis(2-hydroxyethyl)nonandiamide comprising the reaction of azelaic acid or of a diester thereof with ethanolamine in an inert atmosphere, possibly in the presence of an inert solvent.

9. A method according to Claim 8, in which the diester of azelaic acid is dimethyl, diethyl or dipropyl ester, preferably dimethyl ester.

10. A method according to Claim 8 or Claim 9, in which the reaction temperature is between 110°C and 145°C.

11. A method according to any one of Claims 8 to 10 in which the solvent is xylene.

12. A method according any one of Claims 8 to 11, comprising the further step of crystallizing the crude product from isopropanol and subjecting the crystallizate to a crumbling process at approximately 45°C for 4-8 hours and to subsequent gradual cooling to 5-7°C over a period of 10-20 hours.

13. A method according to any one of Calims 8 to 12,

comprising the further consecutive steps of:

(i) drying N,N<sup>1</sup>-bis(2-hydroxyethyl)nonandiamide at a pressure lower than 30 mmHg and at a temperature of between ambient temperature and 40°C for 24-72 hours,

(ii) further drying the product of stage (i) under the same conditions as described above but in a slightly acid atmosphere,

(iii) further drying the product of stage (ii) at a pressure of 1-2 mmHg and at a temperature of 25-40°C for a period of between 1 and 3 days.

14. A method according to Claim 13, in which the acid atmosphere in stage (ii) is achieved by introducing a container containing a 1M solution of sulphuric acid into the dryer.

Intern. .onal Application No  
PCT/IT 99/00258

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 618 842 A (F. DELLA VALLE ET AL) 8 August 1997 (1997-08-08) cited in the application column 22, line 53 -column 24, line 5; claims 1,14; examples 3,4	1,5,8
X	US 5 693 623 A (F. DELLA VALLE ET AL) 2 December 1997 (1997-12-02) column 1; example 2	1,5
A	WO 98 20834 A (TAMARKIN) 22 May 1998 (1998-05-22) claims 13,28	1,5
A	US 3 875 301 A (J. J. WINDHEUSER) 1 April 1975 (1975-04-01) claim 1	1

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

Date of the actual completion of the international search

**28 April 2000**

Date of mailing of the international search report

**15/05/2000**

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

**Voyiazoglou, D**

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IT 99/00258

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 39119 A (NEUTROGENA) 12 December 1996 (1996-12-12) claim 1	5
A	WO 99 17714 A (TELOS) 15 April 1999 (1999-04-15) claim 1	5
A	CHEMICAL ABSTRACTS, vol. 86, no. 4, 24 January 1977 (1977-01-24) Columbus, Ohio, US; abstract no. 21750k, T. REBAGAY ET AL : "Correlation of dielectric constant and solubilizing properties of tetramethyldicarboxamides" page 335; XP002136658 abstract & J. PHARM. SCI., vol. 65, no. 11, 1976, pages 1645-1648,	5

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IT 99/00258

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5618842	A	08-04-1997	IT 1252866 B CA 2086441 A EP 0550008 A JP 5339153 A	28-06-1995 01-07-1993 07-07-1993 21-12-1993
US 5693623	A	02-12-1997	CA 2121952 A US 5696099 A	23-10-1995 09-12-1997
WO 9820834	A	22-05-1998	AU 4880197 A CN 1237151 A EP 0946485 A	03-06-1998 01-12-1999 06-10-1999
US 3875301	A	01-04-1975	NONE	
WO 9639119	A	12-12-1996	AU 708824 B AU 5990396 A BR 9608989 A CA 2223383 A CN 1192134 A CZ 9703870 A EP 0831768 A JP 11507350 T NZ 309677 A PL 323716 A US 5925679 A	12-08-1999 24-12-1996 29-06-1999 12-12-1996 02-09-1998 17-06-1998 01-04-1998 29-06-1999 28-10-1999 14-04-1998 20-07-1999
WO 9917714	A	15-04-1999	IT 1295290 B AU 9542698 A	04-05-1999 27-04-1999

Form PCT/ISA/210 (patent family annex) (July 1992)

BNSDOCID: <WO\_\_0110402A1\_I\_>